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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/939,769	HOEFFLER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-22 and 24-54* is/are pending in the application.

4a) Of the above claim(s) *9-18 and 30-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,19-22,24-29 and 46-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.JD

DETAILED ACTION

1. The amendment filed June 16, 2005 is acknowledged and has been entered. Claims 4, 6, and 22 have been amended.

2. The declaration by Stephen A. Bent filed June 16, 2005 is acknowledged and has been entered.

3. Claims 1-7, 9-22, and 24-54 are pending in the application. Claims 9-18 and 30-45 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim.

4. Claims 1-7, 19-22, 24-29, and 46-54 are currently under prosecution.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed December 16, 2004.

Response to Amendment

8. The amendment filed June 16, 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added

material which is not supported by the original disclosure is as follows: "ER, endoplasmic reticulum *localization* sequence, = SEKDEL(SEQ ID NO:93)" (italics added for emphasis). At page 27, the specification describes the sequence depicted in Figure 2 (i.e., SEKDEL) as an endoplasmic reticulum (ER) *retention* signal; however, there does not appear to be written support for the material added to the brief description of Figure 2, since, in particular, it is not evident that an ER localization signal is equivalent to an ER retention signal.

Applicant is required to cancel the new matter in the reply to this Office Action; or otherwise, this issue might be remedied if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, that are believed to provide written support for the material added to the brief description of Figure 2.

Grounds of Objection and Rejection Maintained

Specification

9. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although Applicant has made a bona fide attempt to resolve this issue, there are additional instances of improperly demarcated trademarks, which include, for example, Molecular Dynamics™ Phosphorimager™ (page 76, line 14).

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The rejection of claims 21, 22, and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 21, 22, and 54 are directed to a vector, which is accorded as ATCC Accession No. 98483.

As noted in the preceding Office action, the disclosure refers to a biological deposit of the vector; see, e.g., page 21 (line 11), page 31 (line 4), and page 46 (lines 17 and 25); however, these references provide insufficient assurance that all required deposits have been made and all the conditions of MPEP § 608.01 (p)(c) are met. See MPEP § 2404.03.

In response to the preceding Office action, Applicant has provided a declaration by Stephen A. Bent that states all restrictions on the availability of the claimed biological material accorded as ATCC Accession No. 98483, which has been accepted as a deposit under the provisions of the Budapest Treaty, will be irrevocably removed upon the granting of a patent upon this application. However, the deposit requirements have still not been entirely satisfied because, while the specification refers to the deposited material, the specification fails to describe the deposit in a manner that fulfils the requirements set forth under 37 CFR § 1.809(d). MPEP § 2411.05 states, in accordance with 37 CFR § 1.809(d), the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited biological material sufficient to specifically identify it and to permit examination. The description also must be sufficient to permit verification that the deposited biological material is in fact that disclosed. Once the patent issues, the description must be sufficient to aid in the resolution of questions of infringement. As a general rule, the more information that is provided about a particular deposited biological material, the better the examiner will be able to compare the identity and characteristics of the deposited biological material with the prior art. Therefore,

appropriate amendment to the specification is required to obviate this issue in its entirety.

Claim Rejections - 35 USC § 103

11. The rejection of claims 1, 20, 24, 27-29, and 47-49 under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,283,173 A in view of Hoeffler et al. (*J. Cell Biochem.* 1994; **190**: 422) is maintained.

At pages 21-24 of the amendment filed June 16, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

At page 21 of the amendment Applicant has argued the prior art does not provide motivation to a skilled practitioner to practice the invention of claim 1. In response to this argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, because the prior art teaches that which is set forth in section 25 of the preceding Office action mailed December 16, 2004, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have used the method of '173 to screen a cDNA library encoding single-chain antibodies to select a clone carrying a cDNA molecule encoding an antibody that binds to a protein of interest, such as a transcription related factor, because '173 teaches the method can be used to identify a cDNA molecule encoding a protein that binds to any protein of interest, including a cDNA molecule encoding antibody, and Hoeffler et al. teaches using the methodology described by '173 to do so. Accordingly, one ordinarily skilled in the art at the time the invention was made would have been motivated to do so

to isolate a cDNA molecule encoding encoding a single-chain antibody that binds to a protein of interest.

Beginning at page 21 of the amendment Applicant has argued that Hoeffler et al. does not provide an enabling disclosure of the claimed invention. Again, U.S. Patent No. 5,283,173 A ('173) teaches a method for screening a cDNA library encoding a protein that binds to another protein of interest using an assay system that is now familiarly known in the art as the "yeast-two-hybrid system"; see entire document (e.g., the abstract; Figures 1 and 2; column 1, lines 15, through column 2, line 14; column 3, lines 40-43; column 5, lines 4-7; the example. Furthermore, '173 teaches the protein of interest is any protein, including, in particular, an antibody; see, e.g., column 1, lines 15, through column 2, line 14; and column 7, lines 42-44. Hoeffler et al. teaches or suggests using the two-hybrid system in yeast, which is described *and enabled* by '173, to screen a cDNA library to select a clone carrying a cDNA molecule encoding *a single-chain antibody* that binds to a protein of interest, such as a transcription related factor.

At page 22 Applicant has contended that Hoefller et al. merely indicates that they have targeted transcription factors for investigation without disclosing that single-chain variable domains of antibodies against transcription factors have been identified, isolated and characterized. In response, it is believed that Applicant's remarks are based upon a misinterpretation of Hoeffler et al. Hoeffler et al. teaches that the system has been used successfully to isolate cDNA molecules encoding single-chain variable regions of antibodies against transcriptional regulatory factors of the CREB/ATF family. Hoeffler et al. then discloses that they have targeted DNA bound transcription factors that are unstimulated under basal conditions with chimeric proteins comprising these single-chain variable domains of antibodies against members of the CREB/ATF family, which are fused to a strong constitutive transcription-activating domain, in order to undertake initial studies with the aim of investigating whether certain members of this family of transcriptional regulatory proteins are endogenously bound to promoters *in vivo* and regulate their activity.

At page 22 of the amendment, Applicant has argued that Hoeffler et al. provides no guidance as to how to generate single-chain antibody-transcriptional activator

chimeric protein libraries. In reply, the artisan of ordinary skill possessed at the time of the invention the skill to make such libraries, since '173 teaches that which is set forth in section 25 of the preceding Office action, including the production of libraries comprised of nucleic acid molecules encoding a chimeric protein comprised of a transcriptional activation domain and *any protein of interest*, including, for example, an antibody (see, e.g., column 1, lines 15, through column 2, line 14; and column 7, lines 42-44).

At page 22, paragraph 4, of the amendment Applicant has remarked that the prior art at the time of filing does not provide a rationale or strategy for overcoming inherent difficulties in using the yeast-two-hybrid system for screening proteins that interact with transcription associated biomolecules. While it is not apparent to which inherent difficulties Applicant has referred, the claimed invention is believed enabled by the prior art.

At page 22, paragraph 4, of the amendment Applicant has disagreed with the statement that the prior art (i.e., '173) teaches the protein of interest may be an antibody. Again, although not expressly teaching the protein of interest may be a single-chain antibody, the prior art does indeed teach or suggest it may be an antibody; see, e.g., column 1, lines 15, through column 2, line 14.

At page 22, paragraph 5, of the amendment Applicant has noted that at the time of the invention, there were other procedures for screening antibodies, such as ELISA, and therefore Applicant has contended that there is no evident rationale for using the more complex yeast-two-hybrid system. In reply, '173 teaches a yeast-two-hybrid system can be used to identify a cDNA molecule encoding a protein that binds to any protein of interest, including a cDNA molecule encoding antibody, and Hoeffler et al. teaches using the methodology described by '173 to do so. Therefore, the ordinarily skilled artisan, at the time the invention was made, would have been motivated to practice the method in order to isolate a cDNA molecule encoding encoding a single-chain antibody that binds to a protein of interest. Moreover, '173 teaches that traditional biochemical methods for identifying proteins that interact with proteins of interest suffer from disadvantages that are overcome by the use of the disclosed methodology; see, e.g., column 1, line 47, through column 2, line 14. In addition, '173 teaches advantages

that are gained by using the disclosed methodology; see, e.g., column 3, line 40, through column 4, line 7.

At page 22, paragraph 6, of the amendment Applicant has argued that '173 does not provide any disclosure or even suggestion to use the disclosed methodology to screen for proteins (e.g., antibodies) that bind transcription associated biomolecules. In reply, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Nonetheless, '173 teaches a yeast-two-hybrid system can be used to identify a cDNA molecule encoding a protein that binds to *any protein of interest*; and Hoeffler et al. teaches using the methodology to screen antibodies that bind transcription associated biomolecules.

At page 23, paragraph 1, of the amendment Applicant has noted that screening for an antibody that binds to transcription-associated molecules would be expected to lead to ambiguities when the assay readout itself is transcription. In reply, although it is unclear how screening for an antibody that binds to transcription-associated molecules would be expected to lead to ambiguities when the assay readout itself is transcription, the prior art teaches that the yeast-two-hybrid system is useful in identifying proteins (the 'prey") that interact with *any other protein* (the "bait"). Moreover, Hoeffler et al. teaches that the system has been used successfully to isolate cDNA molecules encoding single-chain variable regions of antibodies against transcriptional regulatory factors of the CREB/ATF family.

At page 23, paragraph 2, of the amendment Applicant has alleged that using the two-yeast-hybrid system to screen a cDNA library to identify clones encoding single-chain antibodies that bind transcription factors is counter to the conceptual design of the assay system, since the assumption of one skilled in the art would have been that the results of the screen are likely not interpretable. It is unclear why Applicant has made such an allegation, but the Examiner disagrees that the skilled artisan would have assumed that the results of the screen would not be interpretable.

At page 23, paragraph 2, Applicant has remarked that the assumption that using the two-yeast-hybrid system to screen a cDNA library to identify clones encoding single-chain antibodies that bind transcription factors is counter to the conceptual design of the assay system is reasonable due to that fact that the transcription factor that is used as bait in the system used to screen single-chain antibodies could bind DNA sequences that are the same as or different from the DNA binding site to which the DNA binding domain of which the chimeric molecule used as "bait" is comprised. In reply, because Hoeffler et al. teaches its successful use to identify single-chain antibodies against members of a family of transcription factors, binding of a portion of the chimeric "bait" molecules to other DNA sequences by virtue of the DNA binding activity of the transcription factor, as opposed to the activity of the DNA binding domain of which the chimeric molecule used as "bait" is comprised, does not apparently interfere with one's ability to use the claimed invention. Applicant is reminded that the endpoint measured is the transcription of the reporter gene, which is regulated by a promoter comprising the DNA sequences to which the DNA binding domain of the chimeric "bait" molecule binds. Therefore, because of the sensitivity of the assay, binding of a portion of the chimeric "bait" molecules to other DNA sequences by virtue of the DNA binding activity of the transcription factor, as opposed to the activity of the DNA binding domain of which the chimeric molecule used as "bait" is comprised, should not be expected to interfere with one's ability to interpret the data generated using the assay to screen a cDNA library of molecules encoding single-chain antibodies. The absence of reporter gene expression indicates that the clone does not encode a single-chain antibody capable of binding to the transcription factor of which the chimeric bait molecule is comprised; in contrast, expression of the reporter gene strongly suggests the clone encodes an antibody having the sought-after binding activity. Then, it would be obvious to one ordinarily skilled in the art to confirm that the single-chain antibody encoded by the clone identified in screening the cDNA library actually binds the transcription factor using a traditional binding assay (e.g., ELISA).

As to Applicant's concern that the transcription factor of the chimeric molecule used as bait may bind to the same DNA sequences as the DNA binding domain of

which the chimeric molecule is comprised, Hoeffler et al. teaches that the transcription factors to which the single-chain variable antibodies bind are capable of binding promoters without stimulating their activity under basal conditions; if so, under basal conditions, although a portion of the chimeric "bait" molecules may bind to the same DNA sequences to which the DNA binding domain of these molecules bind, by virtue of the DNA binding activity of the transcription factor rather than the activity of the DNA binding domain, this does not apparently interfere with one's ability to use the claimed invention, since, at least, in the instances disclosed by Hoeffler et al., the DNA bound transcription factors to which the antibodies bind fail to activate transcription under such conditions.

Furthermore, it is aptly noted that the claims are not limited to any particular DNA binding domain or any particular DNA sequence to which the DNA binding domain binds; therefore, it is submitted that if it were determined that the inherent activities of the transcription factor used as bait were to include a DNA binding activity that interferes with one's interpretation of the measured endpoint of the assay, it would be obvious to one ordinarily skilled in the art to use a different system comprising a chimeric bait molecule comprising a DNA binding domain that binds a DNA sequence in the promoter upstream of the reporter gene that is not bound by the inherent DNA binding activity of transcription factor of which the molecule is comprised. The "GAL4" system exemplified by the prior art is merely exemplary of the systems that are used to screen cDNA libraries to identify clones encoding proteins that interact with any other protein of interest; for example, '173 teaches many other proteins involved in transcription that also have separable binding and transcriptional activation domains, such as GCN4 and ACR1, are used in such different systems; see, e.g., column 4, line 58, through column 5, line 8. Furthermore, '173 teaches a number of conditions must be met to properly carry out the methodology and in particular teaches that protein of which the chimeric bait molecule is comprises may not carry an activation domain capable of activating transcription of the reporter gene; otherwise the activation domain would allow transcription of the reporter gene as soon as the vector encoding only the chimeric bait molecule is introduced into the host cell; see, e.g., column 7, lines 25-41.

Finally, '173 teaches should any of these conditions necessary for the successful use of the system used not exist, the system may be modified for use by constructing hybrids that carry only portions of the interacting proteins and thus meet those conditions; see, e.g., column 7, lines 25-41. Thus, if the transcription factor of the chimeric molecule used as bait binds to the same DNA sequences as the DNA binding domain of which the chimeric molecule is comprised and thereby interferes with one's ability to use the system to screen a cDNA library to identify a clone encoding a single-chain antibody that binds the transcription factor, it would have been obvious to the ordinarily skilled artisan to modify the system by constructing and using a chimeric bait molecule comprising only an antigenic portion of the transcription factor to which a single-chain antibody may bind, rather than the entire transcription factor, which has an inherent DNA binding activity that would interfere with the use of such methodology otherwise.

At page 23, paragraph 2, Applicant lists additional reasons that they believe the assumption that using the two-yeast-hybrid system to screen a cDNA library to identify clones encoding single-chain antibodies that bind transcription factors is counter to the conceptual design of the assay system is reasonable. It is apparent that Applicant has thought of several situations in which interpreting the results of the assay might be difficult to interpret, but in each instance Applicant is presuming that such situations will arise regardless of the system that is actually used in practicing the claimed invention. As noted above, it would be obvious to one ordinarily skilled in the art to use a system that would provide clear, interpretable results, such that the endpoint measured (i.e., expression of the reporter gene) would strongly suggest the clone emitting the positive signal encodes an antibody having the sought-after binding activity. Then, it would be obvious to one ordinarily skilled in the art to confirm that the single-chain antibody encoded by the clone identified in screening the cDNA library actually binds the transcription factor using a traditional binding assay (e.g., ELISA).

At page 24, paragraph 2, Applicant has asserted that the prior art fails to anticipate all the limitations of claim 20. In reply, the prior art teaches that which is set forth in section 25 of the preceding Office action. Contrary to Applicant's assertion, it

would have been obvious to make a kit comprising a first expression vector; see, e.g., 4, lines 35-44, and column 5, line 28, through column 6, line 52, of '173.

Accordingly, Applicant's arguments have been carefully considered but not found persuasive.

12. The rejection of claims 2-7, 25, 26, 46, and 50-53 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,283,173 A in view of Hoeffler et al. (*J. Cell Biochem.* 1994; **190**: 422) as applied to claims 1, 20, 24, 27-29, and 47-49 above, and further in view of Biocca et al. (*Trends Cell Biol.* 1995 June 5; **5**: 248-252), is maintained.

At pages 25 and 26 of the amendment filed June 16, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

With regard to claim 2, Applicant has argued that there is no motivation in the prior art to combine Biocca et al. with the other references, because Biocca et al. describes antibodies that are targeted to subcellular compartments, whereas Applicant has remarked the yeast-two-hybrid system uses a transcriptional assay in which the bait and prey constructs are not targeted to particular compartments. In response to this argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, because the prior art teaches that which is set forth in section 26 of the preceding Office action mailed December 16, 2004, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have used the method of U.S. Patent No. 5,283,173 A ('173) to screen a cDNA library encoding single-chain antibodies to select a clone carrying a cDNA molecule encoding

an antibody that binds to a transcription related molecule, such as HIV-1 gp100 or Ras, and then to have fused a polynucleotide sequence encoding an intracellular signal peptide that targets the endoplasmic reticulum into the coding frame of the expression vector encoding the fusion protein comprising the single-chain antibody and activation domain and deleted the polynucleotide sequence encoding the activation domain, such that the resultant expression vector encodes a fusion protein comprising the adjoined amino acid sequences of an intracellular signal peptide and a single-chain antibody, because Biocca et al. teaches or suggests that "intracellular immunization", or the intracellular expression of such a fusion protein that binds a transcription related molecule, such as gp100 or Ras, is therapeutic, since expression of the fusion protein that binds gp100 reduces the production of infectious virus and the expression of the fusion protein that binds Ras inhibits signaling by the oncogenic protein. Accordingly, one ordinarily skilled in the art at the time of the invention would have been motivated to do so to clone fusion proteins that bind transcription related molecules, such as gp100 or Ras, because such fusion proteins interfere with the expression and activity the transcription related molecule when expressed intracellularly and targeted to appropriate subcellular compartments.

In addition, because the prior art teaches that which is set forth in section 26 of the preceding Office action, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have manufactured a kit in accordance with the teachings of '173 for use in screening a cDNA library to select a cDNA clone encoding a single-chain antibody that binds transcription related molecules, such as gp100 or Ras, because Biocca et al. teaches such antibodies interfere with the expression and activity of the transcription related molecule. One ordinarily skilled in the art at the time of the invention would have been motivated to do to facilitate screening cDNA libraries to select a cDNA clone encoding a single-chain antibody that binds to a transcription related molecule, such as gp100 or Ras, since kits provide ease, convenience, and reagent uniformity.

Furthermore, contrary to Applicant's assertion, '173 teaches that if eukaryotic host cells are used, such as yeast, the interaction between chimeric bait molecule and

the chimeric prey molecule must be capable of occurring within the yeast nucleus; see, e.g., column 7, lines 25-41. In the preferred example given, the GAL4 activation domain portion of the hybrid containing the second test protein Y (i.e., the prey) must be accessible to the transcription machinery of the cell to allow transcription of the marker gene. Accordingly, because the readout of the assay is the transcription of the reporter gene, measured directly or indirectly, and because transcription occurs in the nucleus of eukaryotic cells, if the host cell used in the system is eukaryotic, contrary to Applicant's assertion, the chimeric proteins encoded by the constructs used in practicing the claimed invention are necessarily targeted to the nucleus of the host cell.

At page 25, paragraph 5, Applicant has asserted with respect to claim 3 that the prior art fails to anticipate the claimed invention. In response, once a cDNA clone encoding a single-chain antibody against the transcription-associated biomolecule has been identified, it would have been obvious to delete the polynucleotide sequences encoding the trans-activation domain of which the chimeric prey molecule was comprised, such that the polynucleotide sequence encoding the single-chain antibody could be used for other purposes, such as those taught or suggested by Biocca et al. or Hoeffler et al.

With regard to claim 4-7, Applicant has asserted that there is no motivation to combine a reference (i.e., Biocca et al.) teaching intracellular immunization "with the screens of the present invention, direct [sic] to isolating antibodies with specificity to the named proteins" (page 25, paragraph 6, of the amendment). In response, Biocca et al. teaches or suggests that "intracellular immunization", or the intracellular expression of such a fusion protein that binds a transcription related molecule, such as gp100 or Ras, is therapeutic, since expression of the fusion protein that binds gp100 reduces the production of infectious virus and the expression of the fusion protein that binds Ras inhibits signaling by the oncogenic protein. Accordingly, one ordinarily skilled in the art at the time of the invention would have been motivated to do so to clone fusion proteins that bind transcription related molecules, such as gp100 or Ras, because such fusion proteins interfere with the expression and activity the transcription related molecule when expressed intracellularly and targeted to appropriate subcellular compartments.

Lastly, at page 25, paragraph 7, Applicant has argued with regard to claims reciting the antigenic portion is not endogenous to the host cell that the methods of Biocca et al. are not analogous to the claimed invention and that the prior art would not motivate *the artisan of average skill in the art of transcriptional regulation* to use the yeast-two-hybrid system to screen for single-chain antibodies against transcription-associated biomolecules that are not endogenous to the host cell. Again, Biocca et al. teaches or suggests that "intracellular immunization", or the intracellular expression of such a fusion protein that binds a transcription related molecule, such as gp100 or Ras, is therapeutic, since expression of the fusion protein that binds gp100 reduces the production of infectious virus and the expression of the fusion protein that binds Ras inhibits signaling by the oncogenic protein. Accordingly, one ordinarily skilled in the art at the time of the invention would have been motivated to do so to clone fusion proteins that bind transcription related molecules, such as gp100 or Ras, because such fusion proteins interfere with the expression and activity the transcription related molecule when expressed intracellularly and targeted to appropriate subcellular compartments. Ras is a transcription-associated biomolecule to which the claims are directed. Therefore, even if it were true, it is of no import that the prior art would not motivate *the artisan of average skill in the art of transcriptional regulation* to use the yeast-two-hybrid system to screen for single-chain antibodies against transcription-associated biomolecules that are not endogenous to the host cell, since the prior art would motivate the artisan of ordinary skill in other relevant arts to do so.

Accordingly, Applicant's arguments have been carefully considered but not found persuasive.

New Ground of Objection

13. Claim 50 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 50, which depends from claim 25, recites, "wherein said antigenic portion is not endogenous to said host cell". This recitation fails to further limit the subject matter of claim 25, which recites, "an antigenic portion [...] that is not endogenous to said host cell".

New Ground of Rejection

14. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,283,173 A in view of Shih et al. (Proc. Natl. Acad. Sci. U S A. 1996 Nov 26; 93 (24): 13896-13901) and Baron et al. (*Gene*. 1992 May 15; **114** (2): 239-243), as evidenced by Apt et al. (*Mol. Gen. Genet.* 1996 Oct 16; **252** (5): 572-579).

U.S. Patent No. 5,283,173 A teaches that which is set forth in section 25 of the preceding Office action mailed December 16, 2004. In particular, the patent teaches a vector comprising a transactivation domain-encoding sequence that includes a means for replicating itself in the host cell (e.g., yeast or mammalian cells) and in bacteria, and also includes a second selectable marker gene that permits selection of cells containing the vector from cells that do not; see, e.g., column 4, line 45, through column 5, line 8; and column 6, lines 9-14. Furthermore, the patent teaches such vectors comprise reporter genes, which are genes encoding drug resistance or metabolic enzymes; see, e.g., column 7, lines 52-64.

On-line Medical Dictionary (published at the Centre for Cancer Education, University of Newcastle upon Tyne ©Copyright 1997-2005 - The CancerWEB Project), which is available on the Internet at http://cancerweb.ncl.ac.uk/omd/, defines the term "shuttle vector" as a "[c]loning vector that replicate in cells of more than one organism, for example E. Coli and yeast [...,] constructed so that they have the origins of replication of the various hosts". Accordingly, the vector described by '173, which includes a means for replicating itself in the host cell and in bacteria, is a "shuttle vector".

However, U.S. Patent No. 5,283,173 A does not expressly teach such a shuttle vector that comprises a nuclear localization signal-encoding sequence, a *constitutive* transactivation domain-encoding sequence, and a zeocin selectable marker gene.

Fields et al. (*Trends Genet.* 1994 Aug; **10** (8): 286-292) (of record) teaches the two-hybrid system as an assay for protein-protein interactions, including the vectors of which the system is comprised, such as a vector comprising a polynucleotide sequence encoding a fusion protein comprising a constitutive transactivation domain (e.g., the activation domain of VP16); see entire document (e.g., page 286, column 1). In particular, Fields et al. teaches that if the DNA binding or activation domains encoded by the different vectors of the system lack an endogenous nuclear localization signal, the vectors include a sequence encoding a heterologous nuclear localization signal.

Baron et al. teaches a shuttle vector comprising a fusion between *sh ble*, which encodes a protein that confers resistance to phleomycin and related antibiotics, and *lacZ*; see entire document (e.g., the abstract; page 241, column 2; and page 242, column 2, through page 243, column 1). Baron et al. teaches that both bacterial and fungal cells transformed with the vector can be positively selected in the presence of antibiotic; see, e.g., the abstract.

Apt et al. teaches the *sh ble* gene from *Streptoalloteichus hindustanus* encodes a protein that also confers resistance to zeocin, which is a derivative of the phleomycin; see entire document (e.g., the abstract). Therefore, as evidenced by Apt et al., the shuttle vector of Baron et al. comprises "a zeocin selective marker gene".

It would have been *pima facie* obvious to one ordinarily skilled in the art at the time of the invention to make a shuttle vector comprising that comprises a nuclear localization signal-encoding sequence, a *constitutive* transactivation domain-encoding sequence, and a zeocin selectable marker gene, because '173 teaches the two-hybrid system, which is used to identify proteins that interact with proteins of interest, comprises a shuttle vector comprising a transactivation domain-encoding sequence and a selectable marker gene, Fields et al. teaches a two-hybrid system comprising a vector encoding a chimeric protein comprising an activation domain that is a constitutive activation domain (i.e., the activation domain of VP16), Fields et al. teaches if the DNA binding or activation domains encoded by the different vectors of the system lack an endogenous nuclear localization signal, the vectors include a sequence encoding a heterologous nuclear localization signal, and Baron et al. teaches a shuttle vector

comprising a "zeocin" selectable marker gene, which enables positive selection in the presence of antibiotic of both bacterial and eukaryotic cells transformed with the vector. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to use the two-hybrid system to identify proteins that interact with proteins of interest.

Conclusion

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
August 24, 2005